Reref to: Gentry LO, Ruskin J, Remington JS: Pneumocystis carinii pneumonia—Problems in diagnosis and therapy in 24 cases. Calif Med 116:6-14, Apr 1972

Pneumocystis Carinii Pneumonia

Problems in Diagnosis and Therapy in 24 Cases

LAYNE O. GENTRY, M.D., JOEL RUSKIN, M.D., AND JACK S. REMINGTON, M.D., *Stanford*

■ *Twenty-four instances of Pneumocystis carinii pneumonia were recognized in 23 patients at the Stanford University Hospitals between 1962 and 1970. The affected persons could be broadly characterized as "compromised" hosts. All but one were receiving immunosuppressive drug therapy for such underlying disease as hematopoietic malignant disease, collagen vascular disorder, and organ transplant rejection. The one patient not receiving immunosuppressant medication had congenital dysgammaglobulinemia and suffered two discrete bouts of pneumocystis pneumonia. Most of the patients were concomitantly infected with other "opportunistic" pathogens.*

Open lung biopsy remained the most reliable method of antemortem diagnosis of pneumocystis infection during this eight-year period. It resulted in little morbidity. Unfortunately, direct examination of appropriately stained sputum specimens for cysts was almost uniformly nonproductive.

The majority of patients received specific antipneumocystis drug treatment (pentamidine isethionate or pyrimethamine and sulfadiazine). "Cure" was achieved when institution of therapy was prompt and duration of therapy approached the empirically recommended two-week course.

The fact that pneumocystis pneumonia can be controlled if recognized early is compelling reason to pursue diagnosis of pneumocystosis in an appropriate clinical setting, namely, in patients with impaired host defenses who have pulmonary infection unresponsive to conventional therapy. There is hope that a noninvasive (serological) technique will be developed shortly to simplify identification of this not uncommon cause of diffuse interstitial pneumonitis.

Postgraduate Fellows, Palo Alto Medical Research Foundation and Division of Infectious Diseases, Department of Medicine, Stanford University School of Medicine (Gentry and Ruskin); and Chief, Allergy, Immunology and Infectious Diseases Division, Palo Alto Medical Research Foundation and Associate Professor of Medicine, Division of Infectious Diseases, Stanford University School of Medicine (Remington).

Supported by The John A. Hartford Foundation, Inc., and the California Division of the American Cancer Society.

Submitted, revised, August 13, 1971.

Reprint requests to: J. S. Remington, M.D., Chief, Allergy, Immunology and Infectious Diseases Division, Palo Alto Medical Research Foundation, 860 Bryant Street, Palo Alto, Ca. 94301.

PNEUMOCYSTIS CARINII may well be the most frequent cause of interstitial pneumonia in patients compromised because of underlying disease or as a result of immunosuppressive chemotherapy.[1] Since this once uniformly lethal infection has recently been shown to respond to drug treatment (pentamidine isethionate),[2,3] prompt recognition in seriously ill persons is no longer just an academic exercise. Consequently, diverse approaches to diagnosis of the infection have been proposed, although none has proved to be totally satisfactory. Most frustrating remains the inability to work with the parasite *in vitro*. This report summarizes our experience in diagnosis as well as management of 24 instances of Pneumocystis carinii pneumonia in 23 patients at the Stanford University Medical Center over an eight-year period.

Clinical Material

All patients were treated at either the Stanford University Medical Center Hospital or the Palo Alto Veterans Administration Hospital. In 11 cases (Cases 1 to 11, Table 1), the patients were in hospital between 1962 and 1967 and were the subject of a previous report.[4,5] In 13 cases (Cases 12 to 24, Table 1) the patients were in hospital between November 1967 and October 1970. Case 14 (Table 1) was also reported separately.[6]

Sputum or tracheal aspirates from patients with diffuse interstitial pneumonia were cultured for bacteria and fungi by conventional methods. They were also smeared on microscope slides which were then fixed in 10 percent formalin and stained with Gomori's methenamine silver nitrate. When these measures failed to reveal a cause for the pneumonia, either thoracotomy with lung biopsy or percutaneous needle lung biopsy under fluoroscopic control was performed. Imprint smears from lung biopsy or autopsy material were also stained with methenamine silver.

If an antemortem diagnosis of Pneumocystis carinii infection was made, treatment with pentamidine isethionate, 4 mg per kg of body weight per 24 hours intramuscularly, was begun immediately and continued for 14 days if the patient survived that long.

Results

The pertinent clinical data relating to each of the cases of pneumocystosis in this series are recorded in Table 1. (The number of cases in each category of underlying disease is shown in Table 2.) Twenty-two of the 23 patients were receiving immunosuppressive chemotherapy for periods ranging from three weeks to seven years preceding diagnosis of P. carinii infection. The remaining patient, a child with congenital dysgammaglobulinemia, was not receiving immunosuppressants. Two separate bouts of pneumocystis pneumonia occurred in this patient[6] (Cases 14 and 18, Table 1). The child first became ill with pneumonia at age nine months. Pneumocystosis was suspected because his male sibling had died two years earlier with pneumocystis disease proved by autopsy. Open lung biopsy confirmed the presence of pneumocystis infection in the child and he responded to a 14-day course of pentamidine therapy. Approximately two and a half years later this same child was again admitted to hospital with pneumonia and a second thoracotomy with lung biopsy was promptly performed. Typical pneumocystis pneumonia was noted in the biopsy specimen and the child was successfully treated with a second 14-day course of pentamidine.

TABLE 2.—*Underlying Diseases in 24 Cases of Pneumocystitis carinii Pneumonia*

Disease	*No. Cases*
Leukemia, Acute and Chronic	6
Reticulum Cell Sarcoma	5
Hodgkin's Disease	4
Systemic Lupus Erythematosus	3
Transplant Rejection*	3
Congenital Dysgammaglobulinemia	2†
Lymphosarcoma	1

*Two cardiac and one renal
†Two separate infections in the same patient

The techniques employed to diagnose pneumocystosis in our patients are listed in Table 3. Open lung biopsy was performed nine times and was positive on each occasion. Thus, in this series there were no instances in which a premortem open lung biopsy was negative and organisms were found at autopsy. In contrast was our experience with closed percutaneous needle biopsy of the lung. This procedure was performed in seven patients, and in three of them no organisms were seen in the biopsy specimen. However, imprint smears of lung tissue obtained at autopsy from these three patients contained many pneumocystis organisms. Moreover, there were no major complications in patients under-

TABLE 1.—*Clinical and Laboratory Findings in Immunosuppressed Patients with Pneumocystis carinii Pneumonia*

Case No.	Age (yrs) Sex	Underlying Disease (duration)	Immunosuppressive Drugs (duration)	Associated Infection†	WBC	Diagnosis: Silver Stains Sputum	Diagnosis: Lung Biopsy	Treatment	Outcome & Remarks
1	53 (M)	Reticulum cell sarcoma (14 yr)	Prednisone (7 mo) cyclophosphamide methotrexate, vincristine (7 mo)	–	5100	(–)	OB(+)*	P+S,** Folinic acid	Died 48 hr after treatment began.
2	41 (M)	Reticulum cell sarcoma (8 yr)	Nitrogen mustard, vincristine, cyclophosphamide (4 mo)	Herpes zoster	2600	ND‡	ND	–	Autopsy diagnosis.
3	44 (M)	Reticulum cell sarcoma (7 yr)	Prednisone (4 yr) cyclophosphamide, vincristine (4 yr)	–	1500	ND	ND	–	Autopsy diagnosis.
4	58 (M)	Reticulum cell sarcoma (2 yr)	Prednisone (2 mo) cyclophosphamide, vincristine, actinomycin D (2 yr)	–	3300	ND	ND	–	Autopsy diagnosis.
5	13 (F)	Systemic lupus erythematosus (8 yr)	Prednisone (7 yr) cyclophosphamide (2 yr)	*Proteus mirabilis* bacteremia	6500	(–)	OB(+)	Pentamidine	Full treatment course. Improvement in pulmonary function. No evidence of pneumocystis at autopsy months later.
6	39 (F)	Systemic lupus erythematosus (5 yr)	Prednisone (5 yr) cyclophosphamide (1 mo)	CMV§ pneumonitis	5000	ND	PC(–)§§	–	Partial pneumothorax—chest tube. Autopsy diagnosis.
7	23 (F)	Systemic lupus erythematosus (3 yr)	Prednisone (3 yr) nitrogen mustard (1 mo)	Candidiasis, disseminated; CMV pneumonitis	21,500	ND	PC(–)	–	Partial pneumothorax—chest tube. Autopsy diagnosis.
8	35 (M)	Hodgkin's disease (15 yr)	Prednisone (4 yr) chlorambucil, vinblastine, cyclophosphamide (7 yr)	–	3200	(–)	OB(+)	–	Died 72 hr after lung biopsy.
9	34 (F)	Hodgkin's disease (11 yr)	Prednisone (3 mo) cyclophosphamide, vinblastine, methylhydrazine (5 yr)	–	6300	ND	ND	–	Autopsy diagnosis.
10	68 (M)	Chronic lymphatic leukemia (19 mo)	Prednisone (3 mo) chlorambucil (1 yr)	Cryptococcal meningitis	17,000	(–)	OB(+)	P+S, Folinic acid	Histological evidence of decreased involvement with pneumocystis; no clinical improvement. Died 4 days after therapy began.
11	26 (F)	Renal transplant rejection (2 mo)	Prednisone (2 yr) azathioprine, actinomycin D (2 mo)	Staphylococcal bacteremia	1700	ND	ND	–	Autopsy diagnosis.
12	42 (M)	Cardiac transplantation	ALG# Immuran, prednisone (2 mo)	CMV pneumonitis	2400	(+) (TA¶)	ND	Pentamidine	Died 48 hr after treatment began; pneumocystis in lungs at autopsy.

13	54 (F)	Cardiac transplantation	ALG Immuran, prednisone (2 mo)	E. coli septicemia; CMV & Bacteroides pneumonitis; disseminated Aspergillus & Toxoplasma	2800	(−)	ND	–	Died; pneumocystis present both lungs at autopsy.
14*	9 mo (M)	Congenital dysgammaglobulinemia	–	–	28,000	(−)	OB(+)	Pentamidine	Survived; 14-day course pentamidine; γ-globulin.
15	40 (F)	Reticulum cell sarcoma (2 yr)	Prednisone (2 mo) cyclophosphamide nitrogen mustard chlorambucil (4 mo)	–	1500	(−)	PC(+)	Pentamidine	Died 72 hr after treatment began; pneumocystis present both lungs at autopsy.
16	25 (M)	Hodgkin's disease (4 yr)	Full course irradiation; prednisone (6 mo)	Candida & CMV pneumonitis; disseminated Aspergillus	17,000	(−)	PC(−)	–	Died; pneumocystis present both lungs at autopsy.
17	51 (M)	Chronic lymphatic leukemia (4 yr)	Prednisone (8 mo) chlorambucil (4 yr)	–	13,000 (89% lymphs)	(−)	PC(+)	Pentamidine	Biopsy complicated by pneumothorax, intrapulmonary hemorrhages; died 11 days after treatment began. No pneumocystis at autopsy.
18*	3 (M)	Congenital dysgammaglobulinemia	–	–	15,000	(−)	OB(+)	Pentamidine	Survived second pneumocystis infection 2 yrs after initial episode.
19	50 (M)	Lymphosarcoma (4½ mo)	Prednisone (4 mo) vincristine cyclophosphamide	Streptococcal septicemia	24,000 (90% lymphs)	(−)	OB(+)	Pentamidine	Died 10 days after treatment began; no pneumocystis at autopsy.
20	17 (M)	Acute lymphocytic leukemia (4 mo)	Prednisone (4 mo) methotrexate	–	480	(−)	ND	Pentamidine	Treated without definite diagnosis; died 36 hr after treatment began; no clinical response; pneumocystis in both lungs at autopsy.
21	43 (F)	Chronic myelogenous leukemia (4 yr. 8 mo)	Myleran (4 yr) chlorambucil (6 mo)	Pneumococcal bacteremia	12,000 (2% myelocytes)	(−)	PC(+)	Pentamidine	Partial pneumothorax-chest tube; 14 day course of pentamidine; infiltrates slowly resolved; survived.
22	68 (F)	Chronic lymphocytic leukemia (8 yr)	Prednisone chlorambucil (6 mo)	–	10,000 (78% lymphs)	(−)	PC(+)	Pentamidine	Partial pneumothorax—no tubes required; died 2 days following full course of treatment; no clinical response; *P. carinii* found at autopsy.
23	16 (M)	Acute lymphocytic leukemia (3 mo)	Cyclophosphamide, vincristine, cytosine arabinoside, prednisone (3 mo)	–	1200 (80 % lymphs)	(−)	OB(+)	Pentamidine	Survived; rapid clearing of symptoms.
24	29 (M)	Hodgkin's disease (9 mo)	Prednisone cytosine arabinoside (8 day)	–	2800	(−)	OB(+)	Pentamidine	Died 6 days after treatment began; no *P. carinii* found at autopsy.

*Open lung biopsy
**Pyrimethamine & sulfadiazine
†Positive cultures or histopathologic evidence
‡Not done
§Cytomegalovirus
§§Percutaneous lung biopsy
¶Tracheal aspiration done at the time of tracheotomy
#Antilymphocyte globulin
★Cases 14 and 18 were in same patient

TABLE 3.—*Diagnostic Procedures in 24 Cases of Pneumocystitis carinii Pneumonia*

Procedure	No. Times Performed	Procedures Positive	Major Complications*
Open Lung Biopsy	9	9	0
Closed Needle Lung Biopsy	7	4	3
Silver Stains of Sputum	17	1	0
Initial Diagnosis at Autopsy	—	10	—

*Greater than 20 percent pneumothorax or intrapulmonary hemorrhage

going an open biopsy procedure (Table 3). However, three patients who had a closed needle biopsy had either significant pneumothorax (greater than 20 percent) requiring a chest tube or significant intrapulmonary hemorrhage. In one patient complications following the needle biopsy were in large part responsible for his death.

Examination of sputum smears proved to be unrewarding in diagnosis of P. carinii pneumonia (Table 3). Only one positive specimen was obtained. This was aspirated from a tracheostomy site in a cardiac transplant patient (Case 12, Table 1). Sputa from 17 of the patients were examined more than once and were consistently negative.

In ten patients the diagnosis of pneumocystis pneumonia was established only at autopsy (Table 3). In four of these ten (Cases 4, 9, 12 and 20, Table 1), the diagnosis was suspected premortem, but biopsy was not performed because these patients were felt to be at the terminal point of their underlying disease. Two of these patients (Cases 12 and 20, Table 1) empirically received antipneumocystis therapy. Two of three patients receiving immunosuppressant drugs for organ transplant rejection died of unsuspected P. carinii pneumonia. However, one of these, a renal transplant recipient (Case 11, Table 1), had concurrent bacteremia due to Staphylococcus aureus. The other patient, a cardiac transplant recipient (Case 13, Table 1), had concurrent infections with E. coli, Bacteroides, Aspergillus, Toxoplasma, and Cytomegalovirus.[7]

Because P. carinii has been found in tissues other than lung (spleen, liver, bone marrow, and lymph node),[8] silver stains of these tissues were examined in six selected patients in this series. No extrapulmonary organisms could be demonstrated.

TABLE 4.—*Concomitant Infections in 11 Patients with Pneumocystitis carinii Pneumonia*

Case No.	Infections
2	Herpes Zoster—Severe Skin Involvement
5	Proteus Mirabilis Bacteremia
6	Cytomegalovirus Infection both Lungs
7	Cytomegalovirus Infection both Lungs, Disseminated Candidiasis (Kidneys, Lungs, Liver and Spleen)
10	Cryptococcal Meningitis
11	Staphylococcal Bacteremia
12	Cytomegalovirus Infection both Lungs
13	E. Coli Septicemia, Cytomegalovirus Infection both Lungs, Bacteroides Infection Left Lung, Disseminated Aspergillus Infection, Toxoplasma Infection of Heart and Brain
16	Candida Infection Left Lung, Disseminated Aspergillus Infection, Cytomegalovirus Infection both Lungs and Liver
19	Streptococcal Bacteremia
21	Pneumococcal Bacteremia

Pneumocystis pneumonia was accompanied by other infections in 11 of the patients (Table 4). Infection with virus (for example, herpes zoster or Cytomegalovirus) either alone or in combination with other infectious agents was encountered in six patients. Bacterial septicemia occurred in five patients, but in four of them positive blood cultures were not detected until after the patients had died. Severe fungus infections with Aspergillus, Candida or Cryptococcus were encountered in four patients and mixed fungus or fungus together with virus infections were common. Disseminated toxoplasmosis was unsuspected in a cardiac transplant patient and, as noted above, it occurred in combination with four other infectious agents.

Twelve courses of pentamidine isethionate and two courses of pyrimethamine and sulfadiazine were administered in this series for periods ranging from one to fourteen days (Table 5). Five patients survived. Each received pentamidine for at least nine days, and all but one (Case 23, Table 1) received a full 14-day course. This latter patient showed rapid clinical improvement, but the drug was discontinued after the ninth day of therapy because of elevated blood urea nitrogen. The patient continued to improve, and the blood urea nitrogen level returned to normal within three days. Among the four remaining successfully treated cases were the two episodes of P. carinii pneumonia occurring in the same patient (Cases 14 and 18, Table 1) with congen-

TABLE 5.—*Results of Therapy in 14 Cases of Pneumocystis Pneumonia*

Results	No. Cases	Treatment Period (days) 1-9	10-14
Equivocal or No Clinical Response; Patient Expired; P. carinii Present at Autopsy	6*	5	1
Clinical Response; Death before Therapy Completed; P. carinii Not Present at Autopsy	3	1	2
Clinical Response; Completed Therapy	5	—	5

*Includes 2 patients treated with pyrimethamine and sulfadiazine.

ital dysgammaglobulinemia. To our knowledge, this is the first instance of successful treatment of two separate bouts of P. carinii pneumonia with pentamidine.

Three patients treated with pentamidine improved clinically but died before a full course of therapy was completed. One patient (Case 24, Table 1) died on the sixth day of pentamidine therapy. Initial clinical improvement was followed by increasing respiratory distress and death. At autopsy there was interstitial pneumonitis with extensive intra-alveolar proteinaceous debris in both lungs, but no P. carinii were seen. Another patient (Case 19, Table 1) had recurrence of pulmonary decompensation after initial improvement and died on the tenth day of pentamidine treatment. No P. carinii were found at autopsy in this patient either, but he too had severe bilateral interstitial pneumonitis. A third patient (Case 17, Table 1) died on the eleventh day of pentamidine therapy. The diagnosis of P. carinii in this case was made by percutaneous needle lung biopsy. Pneumothorax followed the biopsy, and, despite treatment with a chest tube, the patient died with recurrent pneumothorax and subsequent respiratory arrest. There was clinical and radiographic evidence of improvement in the interstitial pneumonia during the 11 days of therapy with pentamidine, and at autopsy no parasites were noted. However, a large area of pneumothorax was present as well as extensive intrapulmonary hemorrhage at the site of the needle biopsy.

Four patients receiving pentamidine had no observable clinical response. Three of them died within three days after the beginning of therapy. At autopsy each had severe interstitial pneumonia with large numbers of P. carinii present in the involved lung tissue. The fourth patient, in whom no detectable therapeutic effect of the drug was observed, had an atypical clinical response. This patient (Case 22, Table 1) had a percutaneous needle lung biopsy (positive for P. carinii) performed early in the course of interstitial pneumonia. Pentamidine therapy was begun and continued for 14 days. There was no improvement in the roentgenographic findings during this time and, while she was receiving pentamidine, progressive respiratory distress developed. She died of anoxia on the second day following a full 14-day course of the drug. At autopsy there was severe interstitial pneumonia in both lungs, associated with large numbers of P. carinii.

Because pyrimethamine and sulfadiazine were known to be effective in treating P. carinii pneumonia in experimental animals[9] and since pentamidine isethionate was not readily available before 1967, two patients (Cases 1 and 10, Table 1) were treated with this combination. The results were equivocal, as reported previously.[5,10]

Discussion

Pneumocystis carinii pneumonia has been well documented as a disease entity in patients receiving immunosuppressive chemotherapy for underlying diseases and in children with immunologic deficiency syndromes.[4,5,11,12,13] The 24 episodes of pneumocystosis described in this report occurred in similar clinical settings. Each of the patients had received immunosuppressive drugs except for the child who had hypogammaglobulinemia. Undoubtedly, the type and severity of underlying disease are important factors in the pathogenesis of this infection. However, it is difficult to quantitate these factors, and no such assessment was possible in this series.

Although reports of finding P. carinii in normal lung tissue at autopsy are rare,[14] recent studies in Europe and the Middle East, utilizing direct sputum examination and serologic techniques, suggest that the carriage rate of pneumocystis in children may be as high as 40 percent.[15] These data support the hypothesis that clinical P. carinii infection in the "compromised" host is almost always due to activation of latent infestation rather than to exogenous infection.[4] Because methenamine silver staining of lung tissue obtained at autopsy has not been done

routinely at the Stanford Medical Center, no statistics are available as to the actual incidence of the organism in our hospital population.

Open lung biopsy has been proposed as a safe and most reliable method for obtaining representative tissue in diffuse pulmonary disease.[16,17] This method was used nine times in our series, with success in all instances. Selection of maximally involved tissue for biopsy may in part be responsible for this result. The most frequently reported complications of the procedure, pneumothorax, bleeding and infection,[16] did not occur. The absence of complications in this series and in others may have been due to rigorous clinical evaluation of patients before biopsy. Potentially troublesome underlying problems were either detected and corrected before operation or biopsy was not performed because the risk to the patient was deemed too great.

Recent reports in the literature suggest that closed needle lung aspiration may also be useful in the diagnosis of P. carinii pneumonia.[18,19,20] The fact that three of seven patients who underwent closed needle biopsy in this series had major complications (which may have led to the death of one patient) is in definite contrast to data from most reported studies. Most disturbing in this series was the failure of the closed lung biopsy specimen to disclose P. carinii in three of seven patients in whom the diagnosis was ultimately proven at autopsy. In these three, there was severe diffuse bilateral interstitial disease documented radiographically, and the biopsy specimen was taken from what was considered to be severely involved lung tissue. None of our patients had repeat needle biopsy, and reports in the literature suggest that this may be necessary to obtain a diagnosis.[21] Sampling error may have been responsible for the negative results in the three cases described above. Clinical conditions did not permit antemortem open lung biopsy in these individuals. Such a controlled study is necessary to compare the relative accuracy of the two diagnostic procedures.

Serological methods for recognition of P. carinii have had sporadic use, especially in Europe. A complement fixation test that employs infected human lung tissue as antigen has been reported to be positive in up to 90 percent of children with pneumocystosis.[22] Impurity of the antigen is a major problem with this procedure. Immunofluorescent techniques have also been utilized successfully to demonstrate P. carinii in lung tissue sections.[23,24] However, routine fluorescent antibody testing for the infection is not yet practicable because no uniform method has been adopted for preparing pneumocystis antigen in large quantity.

In work to be reported separately we have investigated an immunofluorescent diagnostic technique which employs pneumocystis antigen derived from rat rather than human sources. Since heavy pulmonary infection with pneumocystis can be induced almost uniformly in Sprague-Dawley rats treated with cortisone,[9] we believe the rat model would provide laboratories with both a standard and readily available reservoir of antigenic material. Imprint smears of cut surfaces of pneumocystis-infected rat lungs made on clean microscope slides, air dried, fixed in ethanol and stored, if desired, at $-20°$ have proved to be an effective and reproducible antigen in an indirect fluorescent antibody test. (The lung antigen may be obtained from animals soon after death or from tissue previously frozen at $-70°$ C for up to two months.)

A variety of sera were tested by this method in our laboratory. The sera came from normal and overtly infected humans (four of these were from early patients in our Stanford series); from normal, "germ-free" and overtly infected rats; and from rabbits previously immunized with rat alveolar lavage aspirates containing large numbers of pneumocystis organisms or with emulsions of minced human or rat lungs infected with the organism. A number of different fluorescein-conjugated antisera were evaluated as well.

The results of the study, although incomplete, suggest that the technique may be of distinct value in diagnosis of pneumocystis infection, since immunofluorescent structures similar morphologically to silver-stained cysts (and possibly trophozoites) of P. carinii have consistently been observed. But the test has not been developed to the point where sera from grossly infected individuals can be entirely segregated from "control" sera on the basis of intensity of fluorescence. The reason for this may lie in the fact that the method is not sensitive enough to detect antibody titer differences in sera derived from clinically infected hosts and "controls" who, in fact, may also be infected, though subclinically, with the parasite.

The efficacy of pentamidine isethionate in the treatment of P. carinii pneumonia has been well documented.[3] Evidence from our series and others further reveals that efficacy is directly related to rapid diagnosis and early treatment. In the five instances of recovery in our group of patients, the diagnosis was suspected immediately. Survival appears to be related also to duration of pentamidine therapy. In this series all five surviving patients received at least nine days of pentamidine, and in one other large series an average of ten days of treatment appeared to have a positive correlation with survival.[3]

It is difficult to assess the role of underlying disease in trying to evaluate effectiveness of pentamidine or other chemotherapeutic agents in pneumocystosis. Patients with acute leukemia have been noted to have a high mortality in other reported series of P. carinii infection.[20] The results in our patients were consistent with this finding. Persons without rapidly fatal underlying disease might be expected to have a better outcome. In particular, the child with congenital dysgammaglobulinemia in our series fits this latter category. He was treated successfully with pentamidine for two separate episodes of P. carinii pneumonia two years apart.[6]

Side effects following administration of pentamidine have been reported to include both local and systemic reactions.[3] Mild reversible azotemia and hypoglycemia have been encountered most frequently. Although these systemic reactions occurred in this series, they did not produce serious complications.

Because alternative effective drugs for the treatment of P. carinii infections are limited, one instance (Case 22) of pentamidine failure encountered in this series was particularly disturbing. The patient died of respiratory insufficiency despite a full 14-day course of the drug. The fact that numerous P. carinii were present in the lung at autopsy suggests that either the patient had overwhelming infection or that the strain of P. carinii was resistant to pentamidine. Because the organism has not been grown *in vitro*, such resistance cannot be proved. Although cases of pentamidine failure have been recorded,[1,3] most deaths have occurred early in the course of the disease rather than after treatment has been completed.

The efficacy of a combination of pyrimethamine and sulfadiazine in treatment of pneumocystosis has been shown in certain animal studies.[9] Before pentamidine isethionate became available, two of our patients were treated with these two agents. Although both patients died, in one there was histological evidence at autopsy of regression of infection.[5] After pentamidine was made available through the Parasitic Drug Service of the National Center for Disease Control, none of our patients was treated with pyrimethamine and sulfadiazine. However, controlled studies comparing the two different drug regimens would be of value, especially now that an intravenous form of pyrimethamine is available from Burroughs-Wellcome.

Consistent with reports of other investigators is the increased incidence of concomitant infections in our patients with pneumocystosis. Infections with viruses, fungi and bacteria are common in patients with the underlying diseases which are also associated with P. carinii, making any conclusions as to the significance of their association with pneumocystosis difficult. There is no proof that any of these opportunistic infectious agents potentiates development of the others.

Because clinical experience with P. carinii in the United States has been limited to the last decade, there is inadequate knowledge of the host-parasite relationship in this disease. In infections caused by bacteria, fungi, viruses and other protozoa, specific animal models have been adapted to quantitate number of organisms and route of inoculation necessary to produce disease of various organs. Because P. carinii has not been adapted to *in vitro* culture techniques, no experimental challenge studies with this parasite are available. Thus, there are no guides as to number of organisms necessary to cause disease. Clinical experience with several patients in this series further illustrates how this lack of knowledge makes it difficult to evaluate severity of infection in each patient. In several patients, there were large numbers of parasites present in all alveoli on biopsy, yet their response to drug therapy was rapid; whereas in others, whose biopsy specimens contained very few parasites, the clinical picture was that of overwhelming infection. In several instances, patients with totally different clinical courses had similar underlying disease and had received comparable immuno-

suppressive chemotherapy. Thus, further studies of host-parasite interaction and virulence of the parasite are crucial to improved understanding of this unusual infectious process. These studies must await development of more sophisticated culture techniques and an *in vitro* model.

REFERENCES

1. Goodell B, Jacobs JB, Powell RD, et al: Pneumocystis carinii: The spectrum of diffuse interstitial pneumonia in patients with neoplastic diseases. Ann Intern Med 72:337-340, 1970

2. Johnson HD, Johnson WW: Pneumocystis carinii pneumonia in children with cancer. JAMA 214:1067-1073, 1970

3. Western KA, Perera DR, Schultz MG: Pentamidine isethionate in the treatment of Pneumocystis carinii pneumonia. Ann Intern Med 73:695-702, 1970

4. Ruskin J, Remington JS: The compromised host and infection—I. Pneumocystis carinii pneumonia. JAMA 202:1070-1074, 1967

5. Ruskin J, Remington JS: Pneumocystis carinii infection in the immunosuppressed host. *In* Hobby GL (Ed): Antimicrobial Agents and Chemotherapy. Am Soc Microbiology, 1967, pp 70-76

6. Gentry LO, Remington JS: Pneumocystis carinii pneumonia in siblings. J Pediatr 76:769-772, 1970

7. Stinson EB, Bieber CP, Griepp RB, et al: Infectious complications following cardiac transplantation in man. Ann Intern Med 74:22-36, 1971

8. Jarnum S, Rasmussen EF, Ohlsen AS, et al: Generalized Pneumocystis carinii infection with severe idiopathic hypoproteinemia. Ann Intern Med 68:138-145, 1968

9. Frenkel JK, Good JT, Schultz JA: Latent pneumocystis infection of rats, relapse, and chemotherapy. Lab Invest 15:1559-1577, 1966

10. Rifkind D, Faris TD, Hill RB Jr: Pneumocystis carinii pneumonia—Studies on the diagnosis and treatment. Ann Intern Med 65: 943-956, 1966

11. Moore DL, Carnahan CE, Mills SD, et al: Pneumocystis carinii pneumonitis complicating leukemia. Mayo Clin Proc 44:162-168, 1969

12. Minielly JA, Mills SD, Holley KE: Pneumocystis carinii pneumonia. Can Med Assoc J 100:846-854, 1969

13. Vogel CL, Cohen MH, Powell RD Jr, et al: Pneumocystis carinii pneumonia. Ann Intern Med 68:97-108, 1968

14. Lyons HA, Vinijchaikul K, Hennigar GR: Pneumocystis carinii pneumonia unassociated with other disease. Arch Intern Med 108:173-180, 1961

15. Post CA, Dutz WF, Fakouhi AT, et al: Prophylaxis and therapy of epidemic infantile Pneumocystis carinii pneumonia. Vth International Congress of Infectious Diseases, 31 August to 5 September 1970, Vienna, Austria, Vol IV, pp 169-176. Verlag der Wiener Medizinischen Akademie, Wien, Austria

16. Gaensler EA, Moister MVB, Hamm J: Open-lung biopsy in diffuse pulmonary disease. N Engl J Med 270:1319-1331, 1964

17. Klassen KP, Andrews NC: Biopsy of diffuse pulmonary lesions—A seventeen year experience. Ann Thorac Surg 4:117-124, 1967

18. Jacobs JB, Vogel C, Powell RD, et al: Needle biopsy in Pneumocystis carinii pneumonia. Radiology 93:525-530, 1969

19. Lillehei JP, Funke JL, Drage CW, et al: Pneumocystis pneumonia—Needle biopsy diagnosis and successful treatment. JAMA 206: 596-600, 1968

20. Johnson HD, Johnson WW: Pneumocystis carinii pneumonia in children with cancer. JAMA 214:1067-1073, 1970

21. Krumholz RA, Manfredi F, Weg JG, et al: Needle biopsy of the lung—Report on its use in 112 patients and review of the literature. Ann Intern Med 65:293-307, 1966

22. Vivell O: Die serologie der interstitiellen pneumonie. Monatsschr Kinderheilkd 108:146-151, 1960

23. Brzosko WJ, Novoslavski A: Identification of Pneumocystis carinii antigens in tissues. Bull Acad Pol Sci (Biol) 13:49-54, 1965

24. Minielly JA, McDuffie FC, Holley KE: Immunofluorescent identification of Pneumocystis carinii. Arch Path 90:561-566, 1970

USE OF ANTIBIOTICS IN TREATMENT OF HUMAN AND DOG BITES

Probably the dirtiest part of the human body is the mouth—not only by verbal response but by culture! One can never be sure what grows there.

In human and dog bites, our advice is to leave the wound open. We save some problems by doing this. We start with a double scrub; we scrub the wound for 15 minutes and then we discard and redrape and double scrub again for ten minutes, a classic surgical preparation. Then in terms of antibiotics, we start with the penicillin A's, usually oxacillin, 500 mg every six hours on an outpatient basis. I think that the penicillin we have been using has been the phenoxymethyl type. If the patient has to be hospitalized, we use 10 to 15 million units intravenously over a 24-hour period. After two or three days the wound, if it is clean, is closed. The Gram stain will tell you whether you need to add an agent specific for some of the negative organisms, the hemophilus and fusiform bacteria. But it's the combination of the spirochetes, the hemophilus, and the fusiforms that really get you into trouble. These should be treated very cautiously. Even in the phase where most other wounds heal quite nicely, dog and human bites are a very treacherous type of injury. We admit all patients with human bites, especially of the hand or face, leave the wounds open and treat them in this manner.

—David R. Boyd, M.D., Chicago

Extracted from *Audio-Digest Surgery*, Vol. 18, No. 8, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057